Section: Contact Information

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Section: Project Requirements and Description

Group: Requirements to submit AOI

A comprehensive review of previously published data has been completed. : **Yes**

The specific aims are clear and focused. : **Yes**

The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator. : **Yes**

The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months. : **Yes**

Project Title : **Risk Score Algorithm to Predict Individual Risk of Future Serious Late Cardiovascular Disease that includes Dose and Dose Volume Metrics for the Whole Heart and Heart Substructures**

Planned research population (eligibility criteria) :
We will use CCSS overall cohort for developing the risk prediction algorithm and independent St. Jude Lifetime cohort for validation.

Proposed specific aims :
Gap in knowledge: Mean whole heart dose has many meanings, e.g. the same mean heart dose can be from a uniform dose across the entire heart, a low dose to a large volume, or a high dose to a small volume. Given the ability of modern radiation therapy (RT) techniques to limit organ exposure and dose, there is a need for a risk score algorithm that includes mean heart dose, dose volume metrics, and dose to cardiac substructures to predict and compare the late treatment-induced cardiovascular risk from individual treatments and different treatment techniques.

Clinical Uses: These data could be directly translated into radiation oncology practice to define specific treatment planning objectives for the heart, e.g., limits for V5, V20, mean dose, maximum dose, and doses to the cardiac substructures, etc. This would be particularly clinically useful to compare different treatment plans, especially in the context of the numerous contemporary planning techniques in use, which can deliver very different dose profiles, e.g., intensity modulated radiation therapy, stereotactic radiosurgery, gamma knife, passive-scattering and pencil beam scanning proton therapies, carbon-ion therapy etc. In the clinic, we often face the question: Is one plan really better than another? A predictive planning tool that allows entry of relevant dose

volume metrics for the heart and heart substructures would be very beneficial. Similarly, given the wide variety of planning techniques that a survivor may have been treated with, a risk score algorithm that allows addition of dose volume data may better inform surveillance/early intervention strategies.

Specific Aim 1: Develop a risk score algorithm based on available baseline cancer treatment and demographic factors to predict individual risk of future serious cardiovascular disease, both in terms of cardiac-related mortality, as well as selected self-reported cardio vascular disease outcomes using utilizing CCSS overall cohort. We will exclude SJLIFE participants who are also part of CCSS cohort from the training model (they will be included in the validation model).

Specific Aim 2: Validate the risk prediction algorithm derived in Aim 1 with an independent cohort of long-term childhood cancer survivors (St. Jude Lifetime Cohort Study [SJLIFE]) whose late effects outcomes and therapeutic exposures are well characterized. Notably, the cardiac dosimetry, dose and dose volume metrics for the whole heart and heart substructures will be calculated using the same heart model and methods as for CCSS.

This proposal differs from related concept proposals:
- Chow et al. 2010 (10-04) in that it will expand upon the radiation therapy model to include dose volume metrics for the whole heart and substructure doses (Chow et al. included mean heart dose and chest body region dosimetry).
- Bates et al. 2016 (16-07) and 2019 (19-16) in that it expands from examining influence of whole heart dose volume metrics and substructure doses to development of a risk prediction model that incorporates these expanded dosimetry data.

Will the project require non-CCSS funding to complete? : **No**
If yes, what would be the anticipated source(s) and timeline(s) for securing funding? :

Group: Does this project require contact of CCSS study subjects for:

Additional self-reported information : **No**

Biological samples : **No**

Medical record data : **No**

If yes to any of the above, please briefly describe. :

Group: What CCSS Working Group(s) would likely be involved? (Check all that apply)

Second Malignancy :

Chronic Disease : **Secondary**

Psychology / Neuropsychology :

Genetics :

Cancer Control :

Epidemiology / Biostatistics : **Primary**

Section: Outcomes or Correlative Factors

Late mortality : **Primary**

Second Malignancy :

Group: Health Behaviors

Tobacco : **Correlative Factors**

Alcohol : **Correlative Factors**
Physical activity : **Correlative Factors**
Medical screening :
Other :
If other, please specify :

Group: Psychosocial

Insurance :
Marriage :
Education :
Employment :
Other :
If other, please specify :

Group: Medical Conditions

Hearing/Vision/Speech :
Hormonal systems :
Heart and vascular : **Primary**
Respiratory :
Digestive :
Surgical procedures :
Brain and nervous system :
Other :
If other, please specify :

Group: Medications

Describe medications :

Group: Psychologic/Quality of Life

BSI-18 :
SF-36 :
CCSS-NCQ :
PTS :
PTG :
Other :
If other, please specify :

Group: Other

Pregnancy and offspring :
Family history : **Correlative Factors**
Chronic conditions (CTCAE v3) : **Primary**
Health status :

Group: Demographic

Age : **Correlative Factors**
Race : **Correlative Factors**
Sex : **Correlative Factors**
Other :
If other, please specify :

Group: Cancer treatment

Chemotherapy : **Correlative Factors**

Radiation therapy : **Correlative Factors**

Surgery :

Section: Anticipated Sources of Statistical Support

CCSS Statistical Center : **Yes**

Local institutional statistician :

If local, please provide the name(s) and contact information of the statistician(s) to be involved. :

Will this project utilize CCSS biologic samples? : **No**

If yes, which of the following? :

If other, please explain :

Section: Other General Comments

Other General Comments :

Dr. Rebecca Howell and Dr. Daniel Mulrooney will be co-principal investigators and will serve as co-mentors for Mr. Shrestha. Dr. Howell will focus on dosimetry and uncertainty analysis for dosimetry. Dr. Mulrooney will mentor on risk and risk prediction aspects of the study.

I agree to share this information with St. Jude : **Yes**